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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/526,106	03/15/2000	Robert F. Balint	PARE.002.01US	9164

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/526,106	BALINT ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 March 2000 and 27 December 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The Response filed August 10, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 63-66 were pending. Applicants canceled claim 66 and amended claims 63-65. Therefore, claims 63-65 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. The rejection under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicants' arguments and/or amendments. All other rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

5. Claims 63-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabled for non-mutant N-terminal β-lactamase fragments that are used in complementation systems that contain an NGR tri-peptide, a $(Gly_4Ser)_3$ linker and a C-terminal β-lactamase fragment are not enabling for mutant N-terminal β-lactamase fragments (e.g.,

$182_{Met \rightarrow Thr}$ mutations) that are used in complementation systems that contain any C-terminal fragment and any linker and any tri-peptide or other variant. This is an enablement rejection.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors may include, but are not limited to:

(1) the breadth of the claims;
(2) the nature of the invention;
(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

(1-2) Breadth of the claims and nature of the invention: The scope of the claim is broad because Applicant do not place any limit on the structure for the first interactor domain and the flexible polypeptide linker.

(3 and 5) The state of the prior art and the level of predictability in the art: The prior art teaches that protein aggregation, folding and binding interactions are inherently unpredictable. It is known in the art that even a single amino acid change can have dramatic effects on the proteins' structure/function. For example, Voet et al. (1990) teach that a single Glu → Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and

assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic and blood flow blockages (see Voet, D. and Voet, J. G. Biochemistry. New York: John Wiley and Sons 1995, pages 126-128, section 6-3A and page 230, column 2, first paragraph). Thus, a person of skill in the art would not be able to predict which mutations (e.g., $182_{Met \rightarrow Thr}$) would provide for an effective complementation system.

In addition, Applicants do not claim the C-terminal β-lactamase fragment, which is essential to the practice of the claimed invention (e.g., see specification, page 5, last paragraph, "The system is characterized by using fragment pairs comprised of a first and a second member the functionally reassemble into a marker protein having a directly detectable signal"). Without the C-terminal β-lactamase fragment, no marker protein would form and, as a result, no signal would be detected. In this regard, it is noted that claims which lack critical or essential subject matter, which is necessary to the practice of the invention, but is not included in the claim(s), including essential compound structure, is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976); and *Ex Part Bhide* (Bd Pat. App. & Int.) 42 USPQ2d 1441.

(4) The level of one of ordinary skill: The level of skill required would be high, most likely at the Ph.D. level.

(6-7) The amount of direction provided by the inventor and the existence of working examples: Applicants disclose only examples of "non-mutant" N-terminal β-lactamase fragments that contain "interaction-dependent" activity (e.g., see Example 6 in specification). Furthermore, these "non-mutant" N-terminal β-lactamase fragments are coupled to essential tri-peptides like NGR, a $(Gly_4Ser)_3$ linker and a C-terminal β-

lactamase enzyme fragment. For example, Applicants state, "However, for both mutants [i.e., referring to combinations of the currently claimed $55_{Lys \rightarrow Glu}$, $62_{Pro \rightarrow Ser}$ and $182_{Met \rightarrow Thr}$ mutations], plating efficiencies were just as high or higher in the absence of the heterolgous interaction i.e., with the jun helix removed. An exhaustive search for more mutations did not turn up any mutants with interaction-dependent activity. Thus, in contrast to the results obtained with random tri-peptides, where activation remained interaction-dependent, adaptive mutations of α197 invariably eliminated interaction dependents" (see specification page 48, lines 3-8, see more generally Example 7) (emphasis added). Complementation systems, however, require "interaction-dependent" activity because without this activity the complementation system could not differentiate between test proteins that interact with one another from those that do not (e.g., the N-terminal and C-terminal fragments would come together regardless of whether the test proteins interact thus negating the usefulness of the complementation system).

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: The Examiner contends that the quantity of experimentation needed to make and or use the invention would be great because Applicants specification provides evidence that the claimed invention will not work (see sections 6-7 above). In addition, Applicants have omitted essential subject matter (see sections 3 and 5 above). Note that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496 & n.23, 20 USPQ2d 1438, 1445 * n.23 (Fed. Cir. 19991).

Response

6. Applicant's arguments directed to the above Enablement rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants argue the five points listed on pages 6 and 7 (e.g., see 4/22/05 Response).

[2] Applicants argue, "In reference to the fourth point, Applicants note that claim 63 currently recites 'a C-terminal β-lactamase enzyme fragment consisting of amino acids 288 to 208 up to amino acid 189 of said β-lactamase sequence.' Therefore, Applicants submit that the current claim language includes a C-terminal β-fragment" (e.g., see 4/22/05 Response, page 7, second to last full paragraph).

[3] Applicants argue, "At page 6, lines 5-9, the specification summarizes the subject invention as a complementation system with fragment pairs that include a cysteine residue or a '1-3 codon' change (such as M182T) ... Example 7 merely demonstrates that in one particular cell type (prokaryotic cells), one particular embodiment of the subject (an α197 fragment having a '1-3 codon' change) fails to show interaction dependent [i.e., doesn't work]. However, Example 7 also demonstrates successful interaction dependent in another embodiment of the invention ... [thus] the results do not contradict the statement that '[a]ppropriate host cells for application of the subject invention include both eukaryotic cells, such as mammalian, yeast and

plant cells, and prokaryotic cells such as bacterial cells" (e.g., see 4/22/05 Response, page 8, paragraphs 1-3).

[4] Applicants argue, "Because a Ph.D. scientist would understand the prokaryotic systems differ from eukaryotic systems, results obtained in prokaryotic cells would not lead a Ph.D. level scientist away from the use of the claimed invention in eukaryotic cells. Rather, after reading Example 7, one skilled in the art would merely be led away from practicing a complementation system in bacteria with an α197 fragment in the absence of a randomized tripeptide" (e.g., see 4/22/05 Response, page 8, paragraph 4).

[5] Applicants argue, "Even assuming arguendo that the Examiner has properly raised a doubt as to the objective truth of Applicants' disclosure ... [Applicants] have overcome the rejection by providing ... the Galarneau et al. reference" (e.g., see 4/22/05 Response, pages 8 and 9).

This is not found persuasive for the following reasons:

[1] The Examiner concedes the first three points as the claims are currently amended for the reasons outlined on page 7, paragraph 1-3.

[2] The Examiner respectfully disagrees. Applicants' claims only set forth the N-terminal β-lactamase fragment, not the C-terminal β-lactamase fragment as purported. The cited portion of the claim to which Applicants refer notably leaves out the words "is able to functionally reconstitute with" prior to their recitation of "a C-terminal β-lactamase enzyme fragment consisting of amino acids 288 to 208 up to amino acid 189 of said β-lactamase sequence." Thus, when read in its entirety, the claim makes clear that any reference to the C-

terminal β-lactamase fragment represents merely "intended use" language, which is not afforded patentable weight.

[3] The Examiner respectfully disagrees. Example 7 contradicts the statement (i.e., "[a]pproriate host cells for application of the subject invention include ... prokaryotic cells") at least with respect to the prokaryotic cells. Furthermore, nothing in Applicants' specification indicates that "failed attempts" in simple prokaryotic systems lead to "preferred" embodiments for complex eukaryotic systems. If anything, Example 7 provides a "teaching away" from the currently claimed invention.

[4] First, the Examiner notes that this assertion is entirely unsupported. Second, Applicants' never set forth any reason why a person of skill in the art (even a Ph.D.) would somehow assume that failed attempts in simply prokaryotic systems would somehow lead to preferred embodiments in more complicated eukaryotic systems. The art also recognizes that mutations are unpredictable (e.g., see argument with regard to Voet above) and, as a result, a person of skill in the art would not conclude that the M182T mutant would work in a eukaryotic system, even though it doesn't work in prokaryotic systems, based on Applicants' limited disclosure in the specification and the known unpredictability in the art.

[5] The Galarneau et al. reference cannot be used to show enablement for the currently claimed invention because it was published after Applicants' filing date (e.g., see MPEP § 2164.05(a), "Specification Must Be Enabling as of the Filing Date"). Thus, Applicants' arguments are moot. The Galarneau et al. reference is not merely being relied upon to show the accuracy of Applicants' disclosure as purported, but to show support for enablement of the currently claimed M182T mutant. Thus, the *In re Marzocchi and Horton* analysis is not

applicable. If it were, then Applicants would not have amended their claims to remove the lysine to glutamic acid substitution at position 55 and proline to serine substation at position 62 embodiments that were not commensurate in scope with the Galarneau et al. reference. In addition, the Examiner notes that Applicants' generic language page 6, lines 5-9 in the specification does not even mention the use of the currently claimed M182T mutant and Example 7 shows that the M182T mutant doesn't work (at least with respect to the prokaryotic systems).

Accordingly, the Enablement rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 63-65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. Claims 63-65 were amended in the 4/22/05 Response. However, applicant did not show where support for these amendments and/or additions can be found. Specifically, the current amendments require "a polypeptide for use in a fragment complementation system *in vitro* or in a eukaryotic system ... consisting essentially of: (1) a first interactor

domain, (2) a flexible polypeptide linker, and (3) an N-terminal β-lactamase fragment, wherein said N-terminal β-lactamase fragment: (a) consists of amino acids 26 to 188 up to amino acid 207 of the following β-lactamase sequence ... (SEQ ID NO: 27)." There is no support for this amendment. Applicants' specification does not describe the use of a polypeptide as described in newly amended claim 63 consisting of SEQ ID NO: 27 in an *in vitro* or eukaryotic system. Applicants only describe their failed attempts to use SEQ ID NO: 27 in an inoperable prokaryotic system (e.g., see Example 7).

When the specification does not use precisely the same terms as used in the current claims (see above), the question then turns to whether the specification directs or guides one of skill in the art to the subject matter that is currently claimed (e.g., see, *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) ("In the absence of blazemarks [that the claimed compounds were of special interest], simply describing a large genus of compounds is not sufficient to satisfy the written description requirement as to particular species or subgenuses."; see also *In re Ruschig*, 379 F.2d 990, 994-95, 154 USPQ 118, 122 (CCPA 1967) wherein the Court held that a broad generic disclosure failed to constitute a description of more narrowly claimed subject matter; see also *Fields v. Conover*, 443 F.2d 1386, 1391, 170 USPQ 276, 280 (CCPA 1971) wherein the Court stated that direction must be expressed in "full, clear, concise, and exact" language; see also *In re Ahlbrecht*, 435 F.2d 908, 911, 168 USPQ 293, 296 (CCPA 1971)). Here, no such "blaze marks" exist that would direct a person of skill in the art to the currently claimed polypeptides. Although the specification indicates that the use of a β-lactamase was a preferred embodiment, it does not indicate that a

$182_{Met \rightarrow Thr}$ mutation (i.e., a peptide that "consists of" the currently claimed SEQ ID NO: 27) would be particularly favorable in a eukaryotic or an *in vitro* system. Thus, the generic language in the specification (e.g., see page 6, lines 5-9, "Functional reconstitution of the fragment pairs into a marker protein can be enhanced by ... introducing 1-3 codon changes within the nucleotide sequence encoding for a member of a fragment pair [i.e., β-lactamase fragment]") would not lead a person of skill in the art to "pick" the $182_{Met \rightarrow Thr}$ mutation because a large number of mutations would be encompassed by this generic language (e.g., amino acids 26 to 188 up to amino acid 207 can each be independently mutated 1-3 times) and Applicants' specification does not indicate that the $182_{Met \rightarrow Thr}$ would be more favorable than any of the other possible mutation (e.g., $26_{His \rightarrow Thr}$, $26_{His \rightarrow Met}$, $27_{Pro \rightarrow His}$, etc.) in a eukaryotic or *in vitro* system. If anything, Applicants specification, "teaches away" from using the currently claimed $182_{Met \rightarrow Thr}$ mutation by exemplifying this as an inoperable embodiment and further stating that "exhaustive search for more mutations did not turn up any mutants with interaction-dependent activity [i.e., operable embodiments]" (e.g., see Example 7). Further, Applicants' specification does not set forth any proposition that would lead a person of skill in the art to believe that mutations that are inoperable in simple prokaryotic systems (i.e., $182_{Met \rightarrow Thr}$ mutation, Example 7) should somehow be rendered operable in the more complicated eukaryotic and/or *in vitro* systems. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
October 25, 2005

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